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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

SUBJECT: PP#9G2200/9H5217. Pirimiphos-methyl on stored grains (corn, wheat, rice, grain sorghum). Amendment of 3/10/83.

TO: Jay Ellenberger, Product Manager #12
Insecticide - Rodenticide Branch
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and

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FROM: Nancy Dodd, Chemist R.J. Hummel for
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THRU: Charles L. Trichilo, Chief
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I.C.I. Americas, Inc. resubmits Sections D and F for PP#9G2200/9H5217 on stored grains (corn, wheat, rice, grain sorghum).

The previously cited RCB deficiencies as listed in the letter to the petitioner dated 8/25/80, the petitioner's response, and RCB's conclusions are listed below. Additional comments or clarifications resulting from the conference of 7/2/80 are in parentheses.

Deficiency #1:

The temporary tolerance regulation and all future permanent tolerance regulations should be expanded to include all free or conjugated phosphorus containing pyrimidines and

free or conjugated hydroxypyrimidine metabolites of pirimiphos-methyl. Submit a revised Section F.

[The tolerance expression should be revised to include the following compounds: pirimiphos-methyl (I), 0-2-ethylamino-6-methyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate (II), 2-diethylamino-6-methyl-pyrimidin-4-ol (IV), 2-ethylamino-6-methyl-pyrimidin-4-ol (V), and 2-amino-6-methyl-pyrimidin-4-ol (VI). There is no need to include metabolites III and VII in the tolerance regulation.]

Petitioner's response to deficiency #1:

The petitioner submits a revised Section F to include "combined residues of the insecticide pirimiphos-methyl, 0-(2-diethylamino-6-methyl-pyrimidin-4-yl) O,O-dimethylphosphorothioate, the metabolite 0-(2-ethylamino-6-methyl-pyrimidin-4-yl) 0,0-dimethylphosphorothioate and, in free and conjugated form, the metabolites 2-diethylamino-6-methyl-pyrimidin-4-ol, 2-ethylamino-6-methyl-pyrimidin-4-ol, and 2-amino-6-methyl-pyrimidin-4-ol."

The petitioner requests that EPA reconsider the need to include conjugates of 0-(2-ethylamino-6-methyl-pyrimidin-4-yl 0,0-dimethylphosphorothioate in the tolerance expression for the following reasons:

1. Metabolism studies do not provide evidence of the formation of conjugates of this compound.

2. If conjugates of this compound were formed, they would be determined after conjugate cleavage as conjugated hydroxypyrimidines.

Conclusion #1:

We concur with the petitioner that there is no evidence of formation of conjugates of 0-(2-ethylamino-6-methyl-pyrimidin-4-yl 0,0-dimethylphosphorothioate. Therefore we will not require inclusion of conjugates of this compound in the tolerance expression.

Deficiency #1 is resolved.

Deficiency #2:

We are unable to determine whether adequate analytical methods are available to enforce tolerances for residues of parent and metabolites II and III in corn, rice, grain sorghum and wheat and for residues of metabolites IV, V and VI in

grains, meat, milk, poultry and eggs. Accordingly, submit validation data (control and recovery values) reflecting recoveries of metabolites from these commodities, including sample chromatograms.

Petitioner's response to deficiency #2.

For analysis of pirimiphos-methyl and 0-(2-ethylamino)-6-methyl-pyrimidin-4-yl) 0,0-dimethylphosphorothiate (metabolite II) in grains, the petitioner refers to the method previously submitted with PP#9G2200, Vol. II, Section D, Reference ID, 4/18/79. No additional validation data for pirimiphos-methyl and metabolite II are submitted.

Conclusion #2.

Validation data (control and recovery values) for parent and 0-2-ethylamino-6-methyl-pyrimidin-4-yl O, O-dimethyl phosphorothioate (II) in corn, rice, grain sorghum, and wheat are still needed.

Deficiency #3:

Suitable analytical methods for the conjugates of metabolites II, III, IV, V, VI and VII in grains, meat, milk, poultry and eggs are needed or submit data showing that the available methods for these metabolites determine conjugates. (The hydrolysis step which releases conjugates can be deleted in milk and eggs. Since 50% of the radioactive residue is free hydroxypyrimidines, the worst case would be 50% conjugated in milk and eggs. Since metabolites III, and VII and conjugates of metabolite II need not be included in the tolerance proposal, no validation data for these metabolites are needed.)

Petitioner's response to deficiency #3.

A method for determination of the 3 hydroxypyrimidine metabolites in grains is submitted. The method is as follows: Extract grain samples with 50% methanol: 0.1M HCl and hexane. Centrifuge. Evaporate the methanol. Neutralize with anhydrous sodium carbonate and buffer the aqueous extracts to pH 7 with a phosphate buffer. Partition with ethyl acetate and butanol using Extrelut columns. Compounds IV and V are partitioned with 1% butanol:ethyl acetate. Compound VI is partitioned with pure butanol. Cleanup is by adsorption chromatography. Determine Compound IV with high performance liquid chromatography (HPLC) using U.V. absorbance monitoring. The HPLC method has been applied to wheat, barley, oat, and rice grains. Determine Compounds IV, V, and VI by gas-liquid chromatography using a nitrogen selective detector after formation of trimethylsilyl derivatives by reaction with N,0-bis (trimethylsilyl)

trifluoroacetamide (BSTFA) in pyridine. The GLC method has been applied to wheat, barley, maize, oats, sorghum, and rice grains. The limit of detection for both the HPLC and GLC methods is 0.1 ppm.

Recoveries obtained by the HPLC method from wheat, barley, oats, and rice at fortification levels of 0.2, 0.5, 1.0, and 2.0 ppm range from 61-93% for Compound IV. Recoveries obtained by the GLC method from wheat, barley, oat, rice, sorghum, and corn grains at fortification levels of 0.2, 0.5, 1.0, and 2.0 ppm range from 61-90% for Compound IV, 71-102% for Compound V, and 81-103% for Compound VI.

The petitioner submitted an analytical method for the hydroxypyrimidine metabolite (2-diethylamino-6-methyl-pyrimidin-4-ol, 2-ethylamino-6-methyl-pyrimidin-4-ol, and 2-amino-6-methyl-pyrimidin-4-ol) in peanuts and animal products in PP#9G2154. The hydrolysis step for conjugates in milk and eggs is deleted as agreed by RCB. The analytical method (#47) is discussed below.

Tissues - Tissues samples are extracted with 50% methanol: 2M HCl. Centrifuge. The extract is shaken with hexane to separate phosphorothioate containing pyrimidines. The methanol is evaporated. The aqueous extract is refluxed while being heated for one hour to hydrolyze hydroxypyrimidine conjugates. The extracts are then neutralized with anhydrous sodium carbonate and buffered with a phosphate buffer. Then the extract is partitioned with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,0-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry.

Recoveries of 2-diethylamino-6-methyl-pyrimidin-4-ol (Compound IV), 2-ethylamino-6-methyl-pyrimidin-4-ol (Compound V), and 2-amino-6-methyl-pyrimidin-4-ol (Compound VI) were determined in animal tissues at fortification levels of 0.10-5.0 ppm. Recoveries in animal tissues (chicken muscle, cow muscle, liver, and kidney) at a fortification level of 0.1 ppm were 64-82% for Compound IV, 78-97% for Compound V, and 48-93% for Compound VI. Recoveries in animal tissues at a fortification level of 0.5 ppm were 70% for Compound IV, 72% for Compound V, and 53-72% for Compound VI.

The limit of detection of the method in tissues is 0.01 ppm.

Milk - Extract milk (20 g) with a mixture of concentrated HCl (5 ml), methanol (25 ml), and hexane (20 ml). Centrifuge. Evaporate the aqueous phase to remove methanol. Then neutralize with 5M sodium hydroxide and solid sodium carbonate. Buffer

the aqueous phase with phosphate buffer and partition with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry. There is no hydrolysis step for milk.

Recoveries of Compounds IV, V, and VI were determined in cow milk at fortification levels of 0.0025-1.0 ppm. Recoveries in milk at a fortification level of 0.1 ppm were 114% for Compound IV, 101% for Compound V, and 99% for Compound VI.

The limit of detection of the method in milk is 0.01 ppm.

Eggs - Extract eggs in a mixture of 90% methanol:10% 2MHCl. Centrifuge. Shake the supernatant with hexane. Evaporate the bottom layer to dryness. Redissolve the residue in a pH 7 phosphate buffer. Partition with butanol using an Extrelut column. After cleanup by adsorption chromatography and reaction with N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA) in pyridine to form trimethylsilyl derivatives, residues are analyzed by gas chromatography-mass spectrometry. There is no hydrolysis step for eggs.

Recoveries of Compounds IV, V, and VI were determined in eggs at a fortification level of 0.05 ppm. Recoveries were 76-118% for Compound IV, 67-112% for Compound V, and 65-106% for Compound VI.

The limit of detection of the method in eggs is 0.01 ppm.

Conclusion #3:

a. The proposed analytical method is adequate to determine residues of the free hydroxypirimidines (Compounds IV, V and VI) in grains. However, since the method does not contain a hydrolysis procedure, we are unable to determine whether it will measure conjugates of the hydroxypyirimidines in grains. We will require either suitable analytical methods for the conjugates of metabolites IV, V and VI in grains or data showing that the available method for these metabolites determines conjugates.

b. Adequate analytical methods are now available for determination of residues of parent, des-ethyl pirimiphos-methyl, and the hydroxypyrimidines in meat, milk, poultry, and eggs.

Deficiency #4:

Since corn may be stored as kernels or on husked cobs, the label should specify application to shelled grain only, or residue data on cobs should be submitted.

Petitioner's response to deficiency #4:

The petitioner submits a revised label specifying application to shelled corn.

Conclusion #4:

Deficiency #4 is resolved.

Deficiency #5:

In the absence of data, we are unable to determine whether food additive tolerances are needed for residues on the milling fractions of sorghum grain. Therefore, a restriction limiting the use to sorghum grain not intended for milling should be added to the label for the temporary tolerance.

Petitioner's response to deficiency #5:

The petitioner submits a revised label specifying the following in the "Remarks and Precautions" section: "Do not treat grain sorghum intended for milling."

Conclusion #5:

Deficiency #5 is resolved.

Deficiency #6:

A temporary tolerance should be proposed for rice hulls. A level of 60 parts per million (ppm) would be adequate.

Petitioner's response to deficiency #6:

The petitioner has submitted a revised Section F with a temporary tolerance proposal for rice hulls at 60 ppm.

Conclusion #6:

Deficiency #6 is resolved.

Deficiency #7:

A temporary tolerance to cover rice bran and polishings should be proposed in terms of "milling fractions."

Deficiency #8:

A temporary tolerance of 50 ppm to cover wheat bran, shorts (screenings) and germ should be proposed in terms of "wheat milling fractions."

Petitioner's response to deficiencia #7 and #8:

The petitioner has submitted a revised Section F with a temporary tolerance proposal for "milling fractions of rice and wheat" at 50 ppm.

Conclusions #7 and #8:

Deficiencies #7 and #8 are resolved.

Deficiency #9:

Tolerances are needed to cover secondary residues in meat, milk, poultry, and eggs. Based on limited metabolism and feeding studies, which are acceptable for the purposes of a temporary permit only, we conclude that the following temporary tolerances would be appropriate: 0.1 ppm in eggs, milk, the meat, fat and meat byproducts (except kidney and liver) of cattle, goats, hogs, horses, poultry and sheep and 0.5 ppm in the liver and kidney of cattle, goats, hogs, horses, poultry and sheep.

Petitioner's response to deficiency #9:

The petitioner has submitted a revised Section F with temporary tolerance proposals for milk, eggs, poultry, meat, fat and meat byproducts of cattle, goats, hogs, horses, and sheep (except liver and kidney) at 0.1 ppm and for liver and kidney at 0.5 ppm.

Conclusion #9:

Deficiency #9 is resolved.

Recommendations

We recommend against the proposed temporary tolerances for the reasons cited in Conclusions 2 and 3a.

For a favorable recommendation, we need the following:

1. Validation data (control and recovery values) for parent and 0-2-ethylamino-6-methyl-pyrimidin-4-yl O,O-dimethyl phosphorothioate in corn, rice, grain sorghum, and wheat.

2. Either suitable analytical methods for the conjugates of the hydroxypyrimidine metabolites (Compounds IV, V and VI) in grains or data showing that the available method for these metabolites determines conjugates.

cc: R.F.
Circu
Reviewer
TOX
EEB
EAB
Petition No. 9G2200/9H5217
FDA
Robert Thompson

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